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Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline

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Received 27 October 2008; accepted for publication 19 November 2008

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Summary

The frequency, characteristics and reversibility of bortezomib-associated peripheral neuropathy were evaluated in the phase III APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial in patients with relapsed myeloma, and the impact of a dose-modification guideline on peripheral neuropathy severity and reversibility was assessed. Patients received bortezomib 1·3 mg/m^2 (days 1, 4, 8, 11, eight 21-d cycles, then days 1, 8, 15, 22, three 35-d cycles); bortezomib was held, dose-reduced or discontinued depending on peripheral neuropathy severity, according to a protocol-specified dose-modification guideline. Overall, 124/331 patients (37%) had treatment-emergent peripheral neuropathy, including 30 (9%) with grade ≥3; incidence and severity were not affected by age, number/type of prior therapies, baseline glycosylated haemoglobin level, or diabetes history. Grade ≥3 incidence appeared lower *versus* phase II trials (13%) that did not specifically provide dose-modification guidelines. Of patients with grade ≥2 peripheral neuropathy, 58/91 (64%) experienced improvement or resolution to baseline at a median of 110 d, including 49/72 (68%) who had dose modification *versus* 9/19 (47%) who did not. Efficacy did not appear adversely affected by dose modification for grade ≥2 peripheral neuropathy. Bortezomib-associated peripheral neuropathy is manageable and reversible in most patients with relapsed myeloma. Dose modification using a specific guideline improves peripheral neuropathy management without adversely affecting outcome.

Keywords: bortezomib, peripheral neuropathy, multiple myeloma, relapsed, dose modification.

In multiple myeloma (MM), peripheral neuropathy is typically sensory and can arise both from the disease itself, presenting as weakness and numbness of the distal limbs, and as a result of therapeutic agents used to treat MM (Kelly *et al*, 1981; Vrethem *et al*, 1993; Ropper & Gorson, 1998; Dispenzieri & Kyle, 2005). Thalidomide (Singhal *et al*, 1999; Plasmati *et al*, 2007), vincristine (Pal, 1999) and platinum compounds, such as cisplatin (Krarup-Hansen *et al*, 2007), are commonly associated with peripheral neuropathy.

First published online 20 January 2009
doi:10.1111/j.1365-2141.2008.07573.x

Peripheral neuropathy is one of the most important side effects associated with the proteasome inhibitor bortezomib, which is approved in the US for the treatment of patients with MM (http://velcade.com/full_prescrib_velcade.pdf) and in the European Union for the treatment of previously untreated patients with MM in combination with melphalan and prednisone. Bortezomib-associated peripheral neuropathy is predominantly sensory. It is recommended that patients receiving bortezomib be monitored for neuropathy symptoms, such as burning sensation, hyper- or hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness (http://velcade.com/full_prescrib_velcade.pdf). Peripheral neuropathy was initially characterised in phase II trials in MM patients as typically small-fibre, axonal sensory neuropathy (Richardson *et al*, 2006). It has also been reported in phase II studies in mantle cell lymphoma (Fisher *et al*, 2006) and Waldenström macroglobulinemia (Chen *et al*, 2007; Treon *et al*, 2007), and shown to be reversible in the majority of patients in studies in front-line (Popat *et al*, 2008; Richardson *et al*, 2009; San Miguel *et al*, 2008) and relapsed/refractory (Richardson *et al*, 2006) MM, as well as Waldenström macroglobulinemia (Chen *et al*, 2007; Treon *et al*, 2007).

In the randomised, phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial in patients with relapsed MM, single-agent bortezomib demonstrated superior efficacy *versus* dexamethasone in terms of time to progression (TTP), response rate and overall survival (OS) (Richardson *et al*, 2005, 2007a). As in other studies, peripheral neuropathy was a common bortezomib-associated toxicity (Richardson *et al*, 2005). The objectives of this analysis were to evaluate the frequency, characteristics and reversibility of peripheral neuropathy in the bortezomib arm of APEX using data from an updated analysis (Richardson *et al*, 2007a). As the dexamethasone arm was halted at the initial analysis (Richardson *et al*, 2005), no direct comparisons between bortezomib and dexamethasone were possible in this updated analysis. APEX was the first trial in which a specific, protocol-specified dose-modification guideline was used for bortezomib-associated neuropathy; this was developed based on experience in the phase II Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) and Clinical Response and Efficacy Study of Bortezomib in the Treatment of Relapsing Multiple Myeloma (CREST) (Richardson *et al*, 2003, 2006; Jagannath *et al*, 2004, 2008). A key aim of the present analysis was therefore to assess the impact of this dose-modification guideline on the incidence and reversibility of bortezomib-associated peripheral neuropathy, and clinical outcomes with bortezomib.

Patients and methods

The design of APEX has been previously described (Richardson *et al*, 2005). Briefly, 333 patients with relapsed MM following 1–3 prior therapies were randomised to the bortezomib (VELCADE®; Millennium Pharmaceuticals, Inc., Cambridge, MA, USA and Johnson & Johnson Pharmaceutical Research & Development L.L.C., Raritan, NJ, USA) arm to receive bortezomib 1·3 mg/m^2 on days 1, 4, 8 and 11 for eight 21-d cycles, and then on days 1, 8, 15 and 22 for three 35-d maintenance cycles. Patients were assessed every 3 weeks for 39 weeks, and then every 6 weeks until disease progression, after which patients were followed every 3 months.

Response/progression were determined using modified European Group for Blood and Marrow Transplantation criteria (Bladé *et al*, 1998). Safety was assessed throughout and until 30 d after the last bortezomib dose. Treatment-emergent adverse events (AEs) were graded using the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI CTC v2.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf); patients with grade ≥2 peripheral neuropathy at baseline were excluded.

All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization and the Guidelines for Good Clinical Practice; each participating study centre obtained Institutional Review Board approval.

Table I. Assessment of peripheral neuropathy using National Cancer Institute Common Toxicity Criteria (NCI CTC), version 2.0.

	Grade				
	0	1	2	3	4
Neuropathy – sensory	Normal	Loss of deep tendon reflexes/paresthesia Normal function	Objective sensory loss/paresthesia Interfering with function but not daily activities	Sensory loss/paresthesia Interfering with daily activities	Permanent sensory loss Interfering with function
Neuropathic pain	None	Mild pain Normal function	Moderate pain Interfering with function but not daily activities	Severe pain Severely interfering with daily activities	Disabling

Evaluation and management of peripheral neuropathy

The safety population, used in this analysis, included 331 patients who received at least one bortezomib dose. Peripheral neuropathy by NCI CTC grade (Table I) was not formally recorded at baseline. Overall incidence and incidence of grade ≥3 treatment-emergent peripheral neuropathy were determined in patient subgroups defined according to age (<65 years, ≥65 years), number (1, >1) and type of prior therapies, baseline glycosylated haemoglobin [≤upper limit of normal (ULN, 6·4%), >ULN] and history of diabetes, which is associated with neuropathy (Casellini & Vinik, 2007). Risk of peripheral neuropathy was assessed according to cumulative bortezomib dose.

Symptoms of peripheral neuropathy were assessed using the neurotoxicity subscale of the Functional Assessment of Cancer Therapy scale/Gynecologic Oncology Group (FACT/GOG-Ntx) (Cella *et al*, 1993; Calhoun *et al*, 2000). This comprises 11 questions evaluating the presence of peripheral neuropathy symptoms on a scale of 0 (not at all) to 4 (very much). Patients completed the questionnaire at baseline, every 3 weeks during treatment, at the end-of-treatment visit (week 42) and at short-term follow-up visits. Patients who scored >0 for questions Ntx1–4, Ntx8 or Ntx9 at baseline were considered to have peripheral neuropathy symptoms.

Table II. Dose-modification guideline for bortezomib-related neuropathic pain and/or peripheral sensory or motor neuropathy (http://velcade.com/full_prescrib_velcade.pdf).

Severity of peripheral neuropathy signs and symptoms	Modification of bortezomib dose and regimen
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce to 1·0 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold treatment until toxicity resolves, then reinitiate at a dose of 0·7 mg/m^2 once weekly
Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue

Grading for this currently recommended dose-modification guideline is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). In APEX, the dose-modification guideline used was the same, but based on NCI CTC version 2.0 grading (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf); in addition, patients experiencing grade 3 peripheral neuropathy with pain were to discontinue bortezomib.

Peripheral neuropathy was managed using a dose-modification guideline developed based on experience in phase II studies (Richardson *et al*, 2006) (Table II). In patients with grade ≥2 peripheral neuropathy, reversibility of the toxicity in terms of time to improvement (severity reduction of at least one NCI CTC grade) or resolution from initial diagnosis was determined.

Response rate, TTP and OS were evaluated in subgroups of patients defined by presence of peripheral neuropathy (any grade and grade ≥2) and management of grade ≥2 peripheral neuropathy using the dose-modification guideline. Time to improvement/resolution was evaluated in these subgroups of patients with grade ≥2 peripheral neuropathy.

Pharmacological interventions were not protocol-specified. Patients who developed peripheral neuropathy received various interventions, including a three-step treatment plan comprising: vitamins and/or nutritional supplements (B complex, carnitine, alpha lipoic acid and folic acid), gabapentin and nortryptiline or duloxetine. Use of these concomitant medications was recorded.

Statistical analysis

Risk of peripheral neuropathy according to cumulative bortezomib dose, time to improvement or resolution of treatment-emergent peripheral neuropathy, and TTP and OS in patient subgroups were determined using the Kaplan–Meier method. The Wilcoxon signed rank test was used to assess change from baseline to end of study in FACT/GOG-Ntx scores; the Wilcoxon rank sum test was used to assess differences between patients who had treatment-emergent peripheral neuropathy and those who did not. P values <0·05 were considered significant.

Results

Demographic and baseline characteristics of patients in the bortezomib arm of APEX have been reported (Richardson *et al*, 2005). Median age was 62 years. Median time since diagnosis was 3·5 years. Patients had received a median of two prior therapies, including thalidomide in 48% and vinca alkaloids in 75%. Fifty nine (18%) patients had baseline glycosylated haemoglobin >ULN or a history of diabetes. Median duration of bortezomib therapy was six cycles; 39% of patients completed at least eight cycles (Richardson *et al*, 2007a). Median follow-up at this analysis was 22 months (44% of patients had died) (Richardson *et al*, 2007a).

Incidence and severity of peripheral neuropathy

Overall, 124/331 (37%) patients had treatment-emergent peripheral neuropathy, including 91 (27%) with grade ≥2, 30 (9%) with grade ≥3 and 2 (<1%) with grade 4. The neuropathy was predominantly sensory; only five (2%) patients had peripheral motor neuropathy (grade 1 in two patients, grade 2 in two, grade 3 in one). Overall incidence and incidence of

Table III. Incidence of treatment-emergent peripheral neuropathy by NCI CTC grade in the population overall ($n = 331$) and in patient subgroups.

	Patients with peripheral neuropathy, *n* (%)		
	Total	Grade 3/4	Requiring discontinuation
Overall incidence			
Peripheral neuropathy NEC*	124 (37)	30 (9)	31 (9)
Incidence of peripheral neuropathy NEC by patient subgroup			
Age ≥65 years ($n = 124$)	45 (36)	11 (9)	12 (10)
Age <65 years ($n = 207$)	79 (38)	19 (9)	19 (9)
>1 prior therapy ($n = 200$)	75 (38)	20 (10)	20 (10)
1 prior therapy ($n = 131$)	49 (37)	10 (8)	11 (8)
1 prior therapy including			
Steroids ($n = 125$)	48 (38)	9 (7)	11 (9)
Alkylating agent ($n = 114$)	40 (35)	8 (7)	8 (7)
Anthracycline ($n = 96$)	38 (40)	7 (7)	7 (7)
Vinca alkaloid ($n = 94$)	36 (38)	7 (7)	7 (7)
Thalidomide ($n = 25$)	11 (44)	2 (8)	3 (12)
Transplantation ($n = 84$)	32 (38)	6 (7)	5 (6)
HgbA1C >ULN ($n = 40$)	15 (38)	3 (8)	4 (10)
HgbA1C ≤ULN ($n = 278$)	107 (38)	26 (9)	26 (9)
History of diabetes ($n = 41$)	12 (29)	2 (5)	2 (5)
No history of diabetes ($n = 290$)	112 (39)	28 (10)	29 (10)
HgbA1C >ULN or history of diabetes ($n = 59$)	19 (32)	3 (5)	4 (7)
HgbA1C ≤ULN and no history of diabetes ($n = 272$)	105 (39)	27 (10)	27 (10)

*Medical Dictionary for Regulatory Activities (MedDRA) high-level term, includes peripheral neuropathy not otherwise specified, peripheral sensory neuropathy, peripheral neuropathy aggravated, peripheral motor neuropathy and neuropathy not otherwise specified.
HgbA1C, glycosylated haemoglobin; NEC, not elsewhere classified; NOS, not otherwise specified; ULN, upper limit of normal.

grade ≥3 peripheral neuropathy in subgroups defined by age, number and type of prior therapies, glycosylated haemoglobin level and diabetes history are shown in Table III. The onset of peripheral neuropathy generally occurred by cycle 5, corresponding to a cumulative bortezomib dose of approximately 26 mg/m^2 (Fig 1); actuarial overall incidence and incidence of grade ≥3 peripheral neuropathy reached a plateau by cycle 8 (cumulative dose of approximately 42 mg/m^2), with an increase in risk of grade ≥3 toxicity of only approximately 4% for this cumulative dose *versus* cycle 5.

At baseline, 221 (67%) patients reported peripheral neuropathy symptoms according to their responses to questions Ntx1–4, 8 and 9 of the FACT/GOG-Ntx questionnaire. Overall incidence of treatment-emergent peripheral neuropathy in

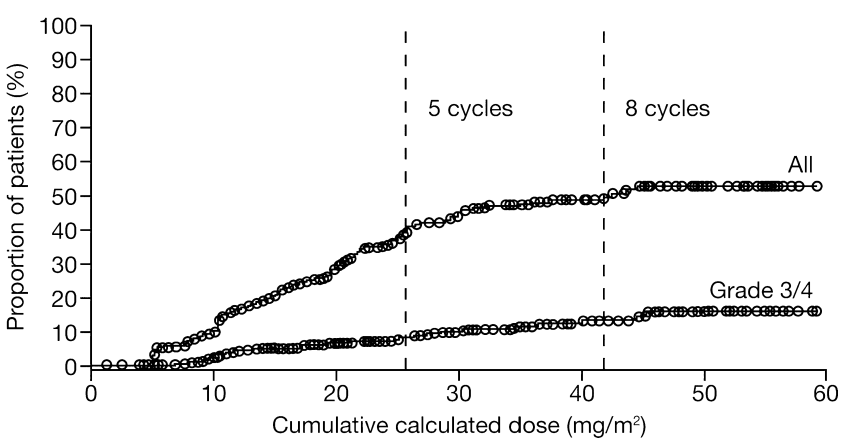

Fig 1. Risk of onset of peripheral neuropathy (all grades and grade 3/4) according to cumulative dose of bortezomib.

Table IV. Functional Assessment of Cancer Therapy scale/Gynecologic Oncology Group (FACT/GOG-Ntx) summary scores at baseline and end of study in all patients, and in patients with or without treatment-emergent peripheral neuropathy.

		FACT/GOG-Ntx summary score				
	n	Median	Range	Mean	SD	*P*-value*
Baseline						
All patients	317	6·0	0–34	7·8	6·72	
Patients without PN	194	6·0	0–34	8·0	7·03	0·453
Patients with PN	123	6·0	0–33	7·3	6·22	
End of study						
All patients	310	9·5	0–44	11·4	8·86	
Patients without PN	187	8·0	0–39	10·6	8·80	0·016
Patients with PN	123	12·0	0–44	12·6	8·83	
Change from baseline to end of study						
All patients†	310	3·0	−21 to +26	3·8	7·31	
Patients without PN†	187	2·0	−18 to +26	2·8	7·44	<0·001
Patients with PN†	123	5·0	−21 to +23	5·3	6·87	

Higher Ntx summary scores indicate greater presence of symptoms of peripheral neuropathy; maximum summary score is 44.
*Comparison of scores in patients with *versus* patients without treatment-emergent peripheral neuropathy, Wilcoxon rank sum test.
†$P \leq 0{\cdot}001$ for change from baseline, Wilcoxon signed rank test.
PN, treatment-emergent peripheral neuropathy.

these patients was 39%, including 11% grade ≥3, compared with 38% and 5% in patients without baseline symptoms. Table IV shows total FACT/GOG-Ntx scores in all patients and in patients who did or did not have treatment-emergent peripheral neuropathy of any NCI CTC grade. There were statistically significant increases in total scores between baseline and end of study in all patients, and in patients who did or did not experience treatment-emergent peripheral neuropathy ($P < 0{\cdot}001$ for all differences). The difference in total score between patients who did or did not have peripheral neuropathy was not statistically significant at baseline ($P = 0{\cdot}453$), but reached significance at the end of the study ($P = 0{\cdot}016$), reflecting a significantly greater increase in patients who experienced treatment-emergent peripheral neuropathy ($P < 0{\cdot}001$).

Reversibility of peripheral neuropathy – impact of dose-modification guideline

Of 91 patients with grade ≥2 peripheral neuropathy, 58 (64%) had experienced improvement ($n = 8$) or resolution ($n = 50$) by their last follow-up prior to data cut-off for this analysis. Median time to improvement or resolution was 110 d (range: 4–627).

In total, 72 of these 91 patients had dose modification per guideline; 31 discontinued due to peripheral neuropathy, including 14 within the first three treatment cycles. Of these 72 patients, 49 (68%) experienced improvement or resolution in a median of 110 d (range: 4–376). Among the 41 patients who had dose modification but did not discontinue bortezomib, 29 (71%) had resolution of their peripheral neuropathy in a median of 78 d (range: 9–376), while among the 31 patients who discontinued, 20 (65%) experienced improvement ($n = 8$) or resolution ($n = 12$) in a median of 122 d (range: 4–296).

In comparison, among 19 patients with grade ≥2 peripheral neuropathy who did not have dose modifications per guideline, a protocol violation, nine (47%) experienced resolution, in a median of 106 d (range: 5–627).

Table V. Impact of dose modification for peripheral neuropathy on response rate, time to progression (TTP) and overall survival (OS).

	Response rate (CR + PR), % (*n*/*N*)	CR rate, % (*n*/*N*)	Median TTP (95% CI), months	Median OS (95% CI), months
All patients ($N = 333$)	43 (135/315)	9 (27/315)	6·2 (5·5, 6·9)	29·7 (23·2, NE)
Patients without peripheral neuropathy ($n = 207$)	38 (75/196)	6 (12/196)	5·6 (4·2, 6·5)	23·2 (20·4, NE)
Patients with peripheral neuropathy ($n = 124$)	50 (60/119)	13 (15/119)	6·9 (5·7, 8·1)	NE (27·8, NE)
Patients with grade ≥2 peripheral neuropathy ($n = 91$)	50 (43/86)	14 (12/86)	6·3 (5·6, 7·7)	NE (22·7, NE)
Patients who had dose modification ($n = 72$)	59 (40/68)	16 (11/68)	6·9 (5·7, 9·1)	NE (23·8, NE)
Patients who had dose hold or reduction ($n = 41$)	60 (24/40)	13 (5/40)	6·9 (6·2, 9·6)	NE (22·7, NE)
Patients who discontinued ($n = 31$)	57 (16/28)	21 (6/28)	6·9 (4·9, 12·6)	NE (18·8, NE)
Patients who did not have dose modification ($n = 19$)	17 (3/18)	6 (1/18)	2·9 (2·2, 4·8)	14·9 (9·2, NE)

NE, not estimable.

Effect of dose modification for peripheral neuropathy on outcome

Response rate, TTP and OS among patients who had peripheral neuropathy and according to use of dose modification for grade ≥2 peripheral neuropathy are presented in Table V. Occurrence of grade ≥2 peripheral neuropathy and use of dose reductions or discontinuation per the dose modification guideline did not appear to adversely affect response rate, median TTP or median OS. Response rate, TTP and OS appeared greater in patients who had grade ≥2 peripheral neuropathy compared with those who did not report peripheral neuropathy, although patient numbers in each group were too small to draw definitive conclusions. Responding patients received prolonged treatment regardless of whether they did (median 9·5 cycles) or did not (median 10 cycles) report peripheral neuropathy; non-responders received a median of 4 cycles.

Pharmacologic interventions

Patients received various interventions for peripheral neuropathy; only gabapentin ($n = 56$) was administered to more than ten patients. Thus, insufficient data were available for a comprehensive analysis of the impact of interventions, but gabapentin administered at recommended doses was reported by individual investigators to be effective in treating neuropathic pain in the majority of treated patients.

Discussion

The results of this analysis as part of the phase III APEX trial in patients with relapsed MM demonstrate the utility of the protocol-specified dose-modification guideline for managing bortezomib-associated peripheral neuropathy and confirm that this toxicity is reversible in the majority of patients. Furthermore, our findings indicate that use of dose modification for peripheral neuropathy does not adversely affect efficacy or outcome with bortezomib in this setting. Therefore, use of the approved bortezomib dose of 1·3 mg/m^2, with dose modification if required to manage toxicity, appears an appropriate dosing strategy. Moreover, this approach appears preferable to the use of a lower bortezomib dose from the start of therapy to minimise peripheral neuropathy, which has been associated with a lower response rate (Jagannath *et al*, 2008; Popat *et al*, 2008).

The overall incidence (37% vs. 35%) and incidence of grade ≥2 treatment-emergent peripheral neuropathy (27% vs. 28%) were comparable between APEX and the SUMMIT and CREST phase II trials (Richardson *et al*, 2006). However, the incidence of grade ≥3 peripheral neuropathy was lower in APEX vs. SUMMIT/CREST (9% vs. 13%), possibly due to use of the dose-modification guideline as a similar approach to dose modification for peripheral neuropathy was not specified in SUMMIT/CREST, and/or due to increasing investigator awareness of neuropathy. The incidence of peripheral neuropathy in the dexamethasone arm at the initial analysis of APEX (Richardson *et al*, 2005) was negligible and comparable with data for high-dose dexamethasone in the front-line and relapsed settings (Rajkumar *et al*, 2006, 2008; Weber *et al*, 2007).

Onset of peripheral neuropathy was similar between APEX and SUMMIT/CREST (Richardson *et al*, 2006), with the toxicity typically emerging by the end of cycle 5 and the risk according to cumulative bortezomib dose subsequently reaching a plateau. This suggests that bortezomib-associated peripheral neuropathy is cumulative and dose-related but only up to a cumulative dose of approximately 26 mg/m^2, beyond which the risk of onset of peripheral neuropathy appears small.

Consistent with observations in SUMMIT/CREST (Richardson *et al*, 2006), incidence and severity of peripheral neuropathy in APEX appeared unaffected by age or prior therapy with other neurotoxic agents. Similarly, glycosylated haemoglobin level and history of diabetes did not substantially affect incidence of peripheral neuropathy; in fact, the incidence of grade ≥3 peripheral neuropathy actually appeared lower in patients with a history of diabetes. These findings lead to the hypothesis that bortezomib-associated neuropathy is mechanistically distinct, and that prior exposure to other neurotoxic agents or history of diabetes should not exclude patients from bortezomib therapy due to concerns about an increased neurotoxicity risk, although this needs to be studied prospectively. However, some caution is warranted as patients with grade ≥2 peripheral neuropathy were excluded from APEX, and so the trial population did not include patients with substantial pre-existing peripheral neuropathy due to previous therapies or coexisting morbidities. In particular, thalidomide can cause permanent nerve damage, and symptoms of thalidomide-associated peripheral neuropathy may only resolve slowly, or not at all, following treatment (http://www.fda.gov/cder/foi/label/2006/021430lbl.pdf), and patients with such neuropathy would have been excluded from APEX.

Monitoring for peripheral neuropathy signs and symptoms is important, especially as there is a small subgroup of patients who develop severe peripheral neuropathy soon after commencing bortezomib. In the APEX study, 45% of patients who discontinued due to grade ≥2 peripheral neuropathy did so within the first three cycles. For these patients, close monitoring during initial treatment and prompt dose modification if required is important to prevent more serious complications and aid reversibility. The FACT/GOG-Ntx questionnaire represents a useful tool for such monitoring (Hausheer *et al*, 2006). In the present analysis, patients who had baseline peripheral neuropathy symptoms, as defined by scores >0 on a subset of FACT/GOG-Ntx questions, appeared to have a higher risk of experiencing grade 3/4 peripheral neuropathy (11%) *versus* patients without baseline symptoms (5%), although overall incidence appeared comparable. Similarly, baseline FACT/GOG-Ntx total scores appeared comparable in patients who did or did not experience treatment-emergent peripheral neuropathy of any grade. As expected, patients with treatment-emergent peripheral

neuropathy had higher FACT/GOG-Ntx scores at study end, and a greater change from baseline, compared with those without the toxicity, indicating some correlation between investigator-assessed peripheral neuropathy and patient-reported symptoms. The increase in FACT/GOG-Ntx score from baseline to study end in patients without treatment-emergent peripheral neuropathy suggests that some patients experienced evolving symptoms of mild neuropathy during bortezomib treatment that did not result in reporting of a treatment-emergent AE, but this was not clinically relevant.

Grade ≥2 peripheral neuropathy was reversible in 64% of patients, with 55% experiencing complete resolution to baseline status. Importantly, management of grade ≥2 peripheral neuropathy per dose-modification guideline appeared to result in a higher proportion of patients experiencing improvement or resolution compared with in patients who did not have dose modification (68% vs. 47%). It is also important to note that the proportion of patients demonstrating reversibility of grade ≥2 peripheral neuropathy was higher at this updated analysis compared with at initial analysis (51%) (Richardson *et al*, 2005), while median time to improvement or resolution was virtually identical [110 vs. 107 d at initial analysis (Richardson *et al*, 2005)]. These data suggest that the proportion of patients experiencing improvement or resolution may further increase with prolonged follow-up.

Outcomes did not appear adversely affected in patients who had dose modification due to peripheral neuropathy. Indeed, response rate appeared higher, and TTP and OS were longer in patients who had peripheral neuropathy. However, this is likely due to the kinetics of bortezomib-associated peripheral neuropathy (Fig 1) and differences in treatment duration according to response, rather than any association between activity/outcome and peripheral neuropathy. Median treatment duration among responding patients and non-responding patients was approximately ten and four cycles respectively, regardless of peripheral neuropathy, demonstrating that the toxicity did not affect overall delivery of bortezomib. Due to the cumulative, dose-related nature of the toxicity (Fig 1), it is therefore not surprising that peripheral neuropathy incidence was higher in responders (60/135, 44%) *versus* non-responders (59/180, 33%). Consequently, response rate was higher in patients with peripheral neuropathy, which may have translated into improved TTP and OS. If non-responders had received similar treatment duration to responders, peripheral neuropathy incidence would probably have been similar between these groups.

Preclinical studies have suggested that bortezomib-associated peripheral neuropathy represents a class effect of proteasome inhibitors (Silverman *et al*, 2006, 2008), although the exact mechanism is still unknown. In mice, the dorsal root ganglia neuronal cell bodies have been suggested as the primary target for peripheral neuropathy associated with proteasome inhibition, with peripheral nerve degeneration occurring later (Silverman *et al*, 2006). Bortezomib disrupts the ubiquitin–proteasome pathway via inhibition of the 26S proteasome (Adams, 2004). *In-vitro* and *in-vivo* studies in mice have demonstrated that proteasome inhibition results in accumulation of ubiquitinated cytoplasmic aggregates, including neurofilaments, in neuronal cells above a threshold of approximately 75% proteasome inhibition (Silverman *et al*, 2006, 2008). A recent neurophysiological study in rats of bortezomib-associated neurotoxicity demonstrated that bortezomib administration resulted in pathological changes in the sciatic nerve and dorsal root ganglia, and induced a significant reduction in sensory nerve conduction velocity (Cavaletti *et al*, 2007). Complete recovery of sensory nerve conduction velocity was seen by the end of the 4-week follow-up period (Cavaletti *et al*, 2007). Additional preclinical studies and clinical evaluations, including nerve conduction studies, nerve biopsies and quantitative sensory testing, are either recently complete or ongoing to establish a better understanding of the nature and characteristics of bortezomib-associated peripheral neuropathy in MM (Richardson *et al*, 2009).

In conclusion, in APEX approximately one-third of patients developed bortezomib-associated peripheral neuropathy, which was dose-related and cumulative up to an incidence plateau, but manageable and reversible in the majority of patients in whom it developed. Prior history of diabetes and neurotoxicity from thalidomide and vincristine did not appear to be risk factors. Use of the dose-modification guideline evaluated in APEX can help improve the management of this toxicity without affecting outcome. Moreover, certain combination therapies are showing reduced overall rates and low rates of significant peripheral neuropathy. For example, in a study of tanespimycin plus bortezomib in relapsed/refractory MM, no grade 3 peripheral neuropathy has been seen, possibly due to upregulation of Heat Shock Protein 70, an observation supported by preclinical evaluation in a rodent model (Richardson *et al*, 2007b). Such combination regimens may hold the promise of lower rates of peripheral neuropathy in this setting.

Acknowledgements

The authors wish to gratefully acknowledge the APEX co-investigators, study teams, and in particular, the patients and families who participated in APEX. The authors would also like to acknowledge the assistance of Steve Hill, Jane Saunders, Caitlin Conant and Nicole Carreau in the preparation of the manuscript.

Research supported by Millennium Pharmaceuticals, Inc., and Johnson & Johnson Pharmaceuticals Research & Development, L.L.C.

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